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Chinese Chemical Letters 21 (2010) 669–673
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Synthesis of thiopyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidines

Essam Kh. Ahmed, Mohamed A. Ameen *

Chemistry Department, Faculty of Science, El Minia University, El Minia 61519, Egypt

Received 23 September 2009

Abstract

Reactions of the 6-hydroxy-thiopyrano[3,4-*c*]pyridine-5-carbonitrile derivative **1** with α-halo-carbonyl compounds gave the ortho-substituted intermediates **2a–c** which were converted into furo[2,3-*b*]thiopyrano[4,3-*d*]pyridines **3a–c** by fusion of a furan moiety under basic conditions. Further cyclization of **3a–c** led to a fusion of a pyrimidine ring, yielding the tetracyclic products **6**, **7** and **8**. In addition, condensation of **6** with various aromatic aldehydes afforded the corresponding imines **9a**,**b**. Mannich reaction of **7** gave products **10a**,**b**.

Keywords: *S*,*N*-Heterocycles; *S*,*N*,*O*-Heterocyles; Furo[2,3-*b*]thiopyrano[4,3-*d*]pyridine; Thiopyranopyridofuropyrimidines

Nitrogen, oxygen, and sulphur containing heterocyclic compounds have received considerable attention due to their wide range of pharmacological activities. The furopyrimidine derivatives are important class of such heterocyclic compounds in pharmaceutical discovery research. Antifungal [1], antifolate [2–4], antibacterial [5], antitumor [3,6], antiviral [7,8], and anti-HCMV (human cytomegalovirus) [9] activities have been described for these compounds.

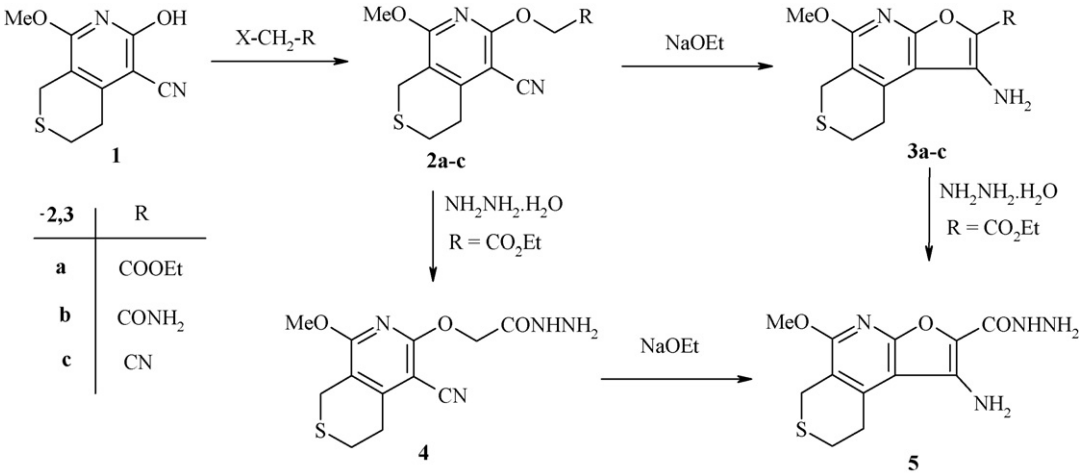
Recently, some furopyrimidines were shown to be potent VEGFR2 (vascular endothelial growth factor receptor 2) and EGFR (epidermal growth factor receptor) inhibitors [10].

Akt, a serine/threonine protein kinase as a viral oncogene, is a critical regulator of PI3K-mediated cell proliferation and survival [11–13]. Since the discovery of human Akt1 (PKB), two additional mammalian Akt isoforms, Akt2 and Akt3, have been identified [14]. One of the intracellular signaling pathways that frequently are activated in cancer cells is the PI3K/Akt kinase pathway [15]. On translocation, Akt is phosphorylated and activated, ultimately resulting in stimulation of cell growth and survival. As an attractive target for the potential treatment of cancer, furo[2,3-*d*]pyrimidines have been investigated as Akt1 kinase inhibitors [16,17] with positive results. As a part of our program toward these small molecule compounds and because of this successive finding we are prompted to synthesize a series of fused furo[3,2-*d*]pyrimidines starting from 3,4-dihydro-6-hydroxy-8-methoxy-1*H*-thiopyrano[3,4-*c*]pyridine-5-carbonitrile.

Reaction of 4-oxo-tetrahydrothiopyran-3-carboxylic acid methyl ester [18] with malononitrile in methanol-benzene containing ammonium acetate and acetic acid would be predicted to afford 3,4-dihydro-6-hydroxy-8-

* Corresponding author.
E-mail address: m_ameen10@yahoo.com (M.A. Ameen).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2009.12.010

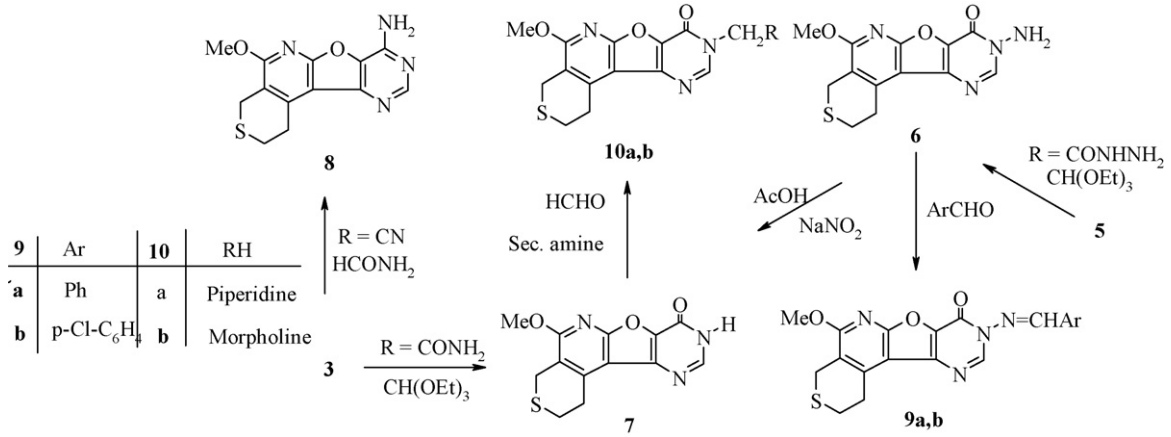


Scheme 1.

methoxy-1*H*-thiopyrano[3,4-*c*]pyridine-5-carbonitrile [19] (**1**), obviously via a mechanism described by Van der Baan and Bichelhaupt [20] for structurally related cyclohexane derivatives. Alkylation of the tautomeric hydroxyl group in such lactams by α-haloester, α-haloamide or α-halonitrile yielded the corresponding α-acidic-3,4-dihydro-6-alkoxy-8-methoxy-1*H*-thiopyrano[3,4-*c*]pyridine-5-carbonitriles **2a**–**c** which are prone to undergo one or more cyclization. In the presence of sodium ethoxide solution, the target systems **3a**–**c**, i.e. the corresponding 1-amino-9,8-dihydro-5-methoxy-6H-furo[2,3-*b*]thiopyrano[4,3-*d*]pyridines, were obtained in a good yields. Treatment of **3a** with hydrazine hydrate afforded 1-amino-8,9-dihydro-5-methoxy-6*H*-furo[2,3-*b*]thiopyrano[4,3-*d*]pyridine-2-carboxylic acid hydrazide (**5**) which could be alternatively obtained from **2a** by initial conversion to the corresponding hydrazide **4** using hydrazine hydrate followed by cyclization in sodium ethoxide solution (Scheme 1).

As illustrated in Scheme 2 compounds **3a-c** were also advantageously used for further cyclization. Treatment of *o*-aminohydrazide **5** with ethyl orthoformate built the pyrimido moiety in compound **6**. Deamination of compound **6** by nitrous acid formed 1,4-dihydro-5-methoxy-2*H*-thiopyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidine-8(9*H*)-one (**7**), which is identical with product obtained in good yield by treatment of **3b** with triethyl orthoformate. Whereas cyclocondensation of **3c** with formamide afforded 4-amino-1,4-dihydro-5-methoxy-2*H*-thiopyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidine (**8**).

Condensation of **6** with various aromatic aldehydes produced the corresponding imines **9a**,**b** in good yields. Reaction of compound **7** with formaldehyde and secondary amines (ambient temperature) yielded the corresponding Mannich-type bases **10a**,**b** in 77–95% yields.



Scheme 2.

In conclusion, an efficient synthesis of furo[3,2-*d*]pyrimidines have been developed, having several merits over hitherto known methods, i.e. fewer reaction steps, mild reaction conditions and higher yields. A number of the obtained products are presently under pharmacological screening.

1. Experimental

Mps have been determined using open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded with a Shimadzu 408 instrument using potassium bromide pellets. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured in DMSO-6 using a Bruker AM 400 with TMS as an internal standard.

*1.1. Synthesis of **2a–c***

1.1.1. General procedures

A mixture of compound **1** (2.2 g, 0.01 mol) and α-haloester, α-haloamide or α-halonitrile (0.01 mol) in DMF (30 mL) was refluxed for 1 h in the presence of anhydrous potassium carbonate (0.01 mol). The reaction mixture was cooled, poured into cold water and stirred for 1 h at room temperature. The product was filtered off and recrystallized from an appropriate solvent.

*1.1.1.1. 3,4-Dihyro-6-(cyano-methyl)oxy-8-methoxy-1H-thiopyrano[3,4-c]pyridine-5-carbonitrile (**2c**).* Colorless crystals from ethanol; Yield (1.98 g, 77%); Mp: 100–101 °C; IR (KBr) υ (cm^{-1}): 2990, 2980, 2210, 1580, 1560; ^{1}H NMR ($CDCl_3$): δ 2.82 (t, 2H, J = 5.6 Hz, H-4), 3.20 (t, 2H, J = 5.6 Hz, H-3), 3.34 (s, 2H, H-1), 4.10 (s, 3H, OCH_3), 5.37 (s, 2H, OCH_3), Calcd. (%) for $C_{12}H_{11}N_3O_2S$ (261.29): C; 55.15, H; 4.24, N; 16.08. Found: C; 54.90, H; 4.10, N; 15.92.

*1.2. Synthesis of **3a–c***

1.2.1. General procedures

To a stirred suspension of compound **2a**, **2b** or **2c** (0.01 mol) in absolute ethanol (20 mL), sodium ethoxide (0.01 mol) was added. Stirring was continued for 15 min and then the reaction mixture was refluxed for another 30 min. The separated solid product was filtered off and recrystallized from an appropriate solvent.

*1.2.1.1. 1-Amino-8,9-dihyro-5-methoxy-6H-furo[2,3-b]thiopyrano[4,3-d]pyridine-2-carboxamide (**3b**).* Yellow crystals from ethanol; Yield (1.8 g, 65%); Mp: 174–175 °C; IR (KBr) υ (cm^{-1}): 3300, 2990, 1655, 1620; ^{1}H NMR ^{1}H NMR (DMSO-d_6): δ 2.90 (t, 2H, J = 5.6 Hz, H-9), 3.40 (t, 2H, J = 5.6 Hz, H-8), 3.60 (s, 2H, H-6), 3.85 (s, 3H, OCH_3), 5.00 (s, 2H, NH_2), 6.70 (s, 2H, $CONH_2$); Calcd. (%) for $C_{12}H_{13}N_3O_3S$ (279.30): C; 51.60, H; 4.69, N; 15.04. Found: C; 51.18, H; 4.33, N; 14.80.

*1.2.1.2. 3,4-Dihydro-6-(hydrazinocarbonylmethyl)-oxy-8-methoxy-1H-thiopyrano[3,4-c]pyridine-5-carbonitrile (**4**).* A mixture of **2a** (1 g, 0.015 mol) and hydrazine hydrate (2 mL) in ethanol (20 mL) was refluxed for 15 min. The reaction mixture was cooled at room temperature. The product was collected by filtration, recrystallized from ethanol to give (0.64 g, 68%) of **4** as colorless crystals. Mp: 193–194 °C; IR (KBr) υ (cm^{-1}): 3300, 2990, 2200, 1680, 1580; ^{1}H NMR ($CDCl_3$): δ 2.85 (t, 2H, J = 5.6 Hz, H-4), 3.10 (t, 2H, J = 5.6 Hz, H-3), 3.60 (s, 2H, H-1), 3.65 (s, 3H, OCH_3), 4.29 (s, 2H, NH_2), 4.65 (s, 2H, OCH_2), 9.40 (s, 1H, NH_2); ^{13}C NMR ($CDCl_3$): δ 22.99 (t, C-4), 23.57 (t, C-3), 29.08 (s, C-1), 54.18 (OCH_3), 68.54 (OCH_2), 86.69 (s, C-5), 110.69 (C-8a), 114.55 (s, CN), 152.74 (C-4a), 160.78 (C-8), 161.18 (C-6), 162.92 (s, C=O); Calcd. (%) for $C_{12}H_{14}N_4O_3S$ (294.33): C; 48.96, H; 4.79, N; 19.03. Found: C; 48.80, H; 4.57, N; 18.90.

*1.2.1.3. 1-Amino-8,9-dihyro-5-methoxy-6H-furo[2,3-b]thiopyrano[4,3-d]pyridine-2-carboxylic acid hydrazide (**5**). Method A*: A mixture of **2a** (0.3 g, 0.001 mol) and hydrazine hydrate (2 mL, 80%) was refluxed in ethanol (5 mL) for 2 h. After cooling the separated solid product filtered off washed with ethanol to give (0.24 g, 82.7%) of **5**. Mp: 248-250 °C; IR (KBr) υ (cm^{-1}): 3400, 3300, 2980, 1660, 1620; ^{1}H NMR (DMSO-d_6): δ 2.90 (t, 2H, J = 5.6 Hz,

H-9), 3.30 (t, 2H, J = 5.6 Hz, H-8), 3.60 (s, 2H, H-6), 3.85 (s, 3H, OCH_3), 4.30 (s, 2H, NH_2), 5.70 (s, 2H, $CONH_2$), 9.20 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 22.96 (t, C-9), 23.69 (t, C-8), 27.02 (s, C-6), 54.12 (OCH_3), 106.39 (C-1), 112.46 (s, C-5a), 123.70 (C-9b), 136.26 (s, C-9a), 143.96 (s, C-2), 155.28 (s, C-3a), 159.83 (s, C-5), 161.08 (s, C=O); Calcd. (%) for $C_{12}H_{14}N_4O_3S$ (294.32): C; 48.96, H; 4.79, N; 19.03. Found: C; 48.80, H; 4.67, N; 18.90.

Method B: Compound **5** obtained from **4** in 85% yield, was spectroscopic ally equivalent with the material separated in method A.

*1.2.1.4. 9-Amino-1,4-dihyro-5-methoxy-2H-thiopyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-d]pyrimidine-8(9H)-one (**6**).* A mixture of **5** (0.3 g, 0.001 mol) and ethyl orthoformate (0.2 g, 0.0017 mol) was heated at 180 °C. The initial melt solidified, triturating and recrystallization of the solid product from aqueous DMF yielded 0.22 g (72.4%) of compound **6**. Mp: 290–291 (Lit. [19], Mp: 294–296).

*1.2.1.5. 1,4-Dihyro-5-methoxy-2H-thiopyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-d]pyrimidine-8(9H)-one (**7**). Method A*: A suspension of compound **6** (0.29 g, 0.001 mol) in 50% aqueous acetic acid (5 mL) was warmed to 45–50 °C and then treated with sodium nitrite (0.14 g, 0.002 mol) in portions. The mixture was heated at 45–50 °C until the evolution of all nitrogen gases ceased. The resulting solution was cooled and diluted with water. The solid product was purified by dissolving in 10% sodium hydroxide solution (3 mL), precipitated by HCl followed and recrystallized from aqueous DMF to give colorless crystals of compound **7**. Yield (0.17 g, 59%). Mp: 310 °C (decomp.); IR (KBr) υ (cm^{-1}): 2980, 1680, 1640, 1600, 1580; ^{1}H NMR (DMSO-d_6): δ 2.90 (t, 2H, J = 5.6 Hz, H-1), 3.40 (t, 2H, J = 5.6 Hz, H-2), 3.60 (s, 2H, H-4), 4.10 (s, 3H, OCH_3), 8.10 (s, 1H, NH), 12.80 (s, 1H, H-10); Calcd. (%) for $C_{13}H_{11}N_3O_3S$ (289.31): C; 53.96, H; 3.83, N; 14.52. Found: C; 53.80, H; 3.68, N; 14.29.

Method B: Compound **7** separated from **3b** in 86% yield is identical in all aspects with that obtained above.

*1.2.1.6. 8-Amino-1,4-dihyro-5-methoxy-2H-thiopyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-d]pyrimidine (**8**).* A mixture of **3c** (0.6 g, 0.0023 mol) formamide (5 mL) and formic acid (3 ml) in DMF (5 mL) was refluxed for 8 h then cooled at room temperature. The resulting solid product was collected by filtration and recrystallized from methanol to yield 0.5 g (86.3%) of **8** as brown crystals. Mp: 318 °C (decomp.); IR (KBr) υ (cm^{-1}): 3300, 2980, 1680, 1640, 1600; ^{1}H NMR (DMSO-d_6): δ 2.90 (t, 2H, J = 5.6 Hz, H-1), 3.30 (t, 2H, J = 5.6 Hz, H-2), 3.55 (s, 2H, H-4), 4.10 (s, 3H, OCH_3), 6.80 (bs, 2H, NH_2), 8.40 (s, 1H, H-10); Calcd. (%) for $C_{13}H_{12}N_4O_2S$ (288.33): C; 54.15, H; 4.20, N; 19.43. Found: C; 54.02, H; 4.06, N; 19.29.

*1.2.1.7. Arylideneamino-1,4-dihyro-5-methoxy-2H-thiopyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-d]pyrimidine-8(9H)-one (**9a**,**b**).* A mixture of **6** (0.3 g, 0.001 mol) and aromatic aldehydes (0.001 mol) in ethanol (10 mL) in presence of catalytic amount of piperidine was refluxed for 30 min. The reaction mixture was concentrated to one-half of its volume then cooled. The solid crystals collected and recrystallized from appropriate solvent.

*1.2.1.8. 9-Benzylideneamino-1,4-dihyro-5-methoxy-2H-thiopyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-d]-pyrimidine-8(9H)-one (**9a**).* Yellow crystals from methanol; Yield (0.28 g, 70%); Mp: 194–196 °C; IR (KBr) υ (cm^{-1}): 3000, 2980, 1700, 1600, 1580; ^{1}H NMR (DMSO-d_6): δ 2.83 (t, 2H, J = 5.6 Hz, H-1), 3.20 (t, 2H, J = 5.6 Hz, H-2), 3.50 (s, 2H, H-4), 4.20 (s, 3H, OCH_3), 7.60–7.80 (m, 5H, Ar-H), 8.40 (s, 1H, H-10), 9.30 (s, 1H, CH=N); Calcd. (%) for $C_{20}H_{16}N_4O_3S$ (392.44): C, 61.21, H; 4.11, N; 14.28. Found: C; 61.04, H; 3.95, N; 14.12.

*1.2.1.9. 9-Substituted-aminomethyl-1,4-dihyro-5-methoxy-2H-thiopyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-d]-pyrimidine (**10a**,**b**).* To a mixture of **7** (0.3 g, 0.001 mol), and secondary amine (0.001 mol), formaldehyde (5 mL) was added. The reaction mixture was stirred at 10–15 °C for 30 min. The separated solid product was filtered off, washed with petroleum ether and recrystallized from methanol.

*1.2.1.10. 9-Piperidine-aminomethyl-1,4-dihyro-5-methoxy-2H-thiopyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-d]-pyrimidine (**10a**).* Pale yellow crystals; Yield (0.3 g, 80%); Mp: 124–126 °C; IR (KBr) υ (cm^{-1}): 2985, 1690, 1610, 1580; ^{1}H NMR (DMSO-d_6): δ 1.65–1.85 (m, 6H), 2.7-2.85 (m, 4H), 2.95 (t, 2H, J = 5.6 Hz, H-1), 3.30 (t, 2H, J = 5.6 Hz, H-2), 3.55 (s, 2H, H-4), 4.10 (s, 3H, OCH_3), 5.15 (s, 2H, CH_2), 8.40 (s, 1H, H-10); Calcd. (%) for $C_{19}H_{22}N_4O_3S$ (386.48): C; 59.05, H; 5.74, N; 14.50. Found: C; 58.88, H; 5.53, N; 14.32.

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